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Velo-Cardio-Facial and Partial DiGeorge Phenotype in a Child With Interstitial Deletion at 10p13—Implications for Cytogenetics and Molecular Biology

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We report on a female with a interstitial deletion of 10p13 and a phenotype similar to that seen with the 22q deletion syndromes (DiGeorge/velo-cardio-facial). She had a posterior cleft palate, perimembranous ventricular septal defect, dyscoordinate swallowing, T-cell subset abnormalities, small ears, maxillary and mandibular hypoplasia, broad nasal bridge, deficient alae nasi, contractures of fingers and developmental delay. This could indicate homology of some developmental genes at 22q and 10p so that patients with the velocardiofacial phenotype who do not prove to be deleted on 22q are candidates for a 10p deletion.

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KEY WORDS: velo-cardio-facial, DiGeorge, chromosome 10, chromosome 22, interstitial deletion

INTRODUCTION

Since the description by Elliot [1970] of an infant with a partial deletion of 10p , 21 other cases of monosomy 10p have been reported. In 17 cases the breakpoint was assigned to p13 [Elstner et al., 1984; Francke et al., 1975; Gencik et al., 1983; Greenberg et al., 1986; Herve et al., 1984; Klep de Pater et al., 1981; Koenig et al., 1985; Monaco et al., 1991; Shokeir et al., 1975; Obregon et al., 1992; Shapira et al., 1994; Lynch et al., 1995]. In three it was determined to be in the area p14 [Bourrouillou et al., 1981; Fryns et al., 1981; Suciu and Nanulescu., 1983], in one it was in the area of p11-15 [Juberg et al., 1981], and in one a definite breakpoint was not mentioned [Elliot et al., 1970].

Other circumstances in which deletion of 10p has been reported previously include seven reports of individuals with the deletion as one finding in a complex of chromosomal anomalies [Kousseff et al., 1992; Lai et al., 1992; Prieto et al., 1978; Slinde and Handsteen, 1982; Turleau et al., 1979].

Deletion 10p13 has been associated with hypoparathyroidism [Greenberg et al., 1984; Gencik et al., 1983; Elstner et al., 1984; Monaco et al., 1991] and the DiGeorge anomaly [Greenberg et al., 1986, 1988a; Herve et al., 1984; Koenig et al., 1985; Monaco et al., 1991; Obregon et al., 1992] as well as with congenital heart disease, facial anomalies (such as small "dysplastic" ears, micrognathia, and facial clefts) urinary tract anomalies, developmental and growth delay including small for gestational age at birth, and hand anomalies [reviewed by Shapira et al., 1994; Obregon et al., 1992].

These manifestations are reminiscent of the Velocardio facial/DiGeorge syndrome [Shprintzen et al., 1981; Lipson et al., 1991; Goldberg et al., 1993]. We report an additional case of partial deletion of 10p; the patient was not deleted at 22q by fluorescent in situ hybridisation techniques, thus indicating velocardio facial/ DiGeorge phenotype can be caused by deletion at 10p13 and of 22q11.

CLINICAL REPORT

The patient is the first child of non consanguineous parents in their mid-twenties. There had been one early miscarriage, cause unknown. She was born at term by caesarean section after an uneventful pregnancy. There was no family history of birth defects or developmental problems.

Birth weight was 2,850 g (<10th centile), length was 46 cm (3rd centile), and head circumference was 33.5 cm (10th centile). She had small "dysplastic" ears, small nose with deficient alae nasi, and maxillary and mandibular hypoplasia (Figs. 1, 2). Finger contractures

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We report with regret the untimely death of Dr. Anthony Lipson, which occurred after this paper was written. Dr. Lipson's enormous enthusiasm and hard work have greatly contributed to the understanding of VCFS to the benefit of many families. We dedicate this paper to him.

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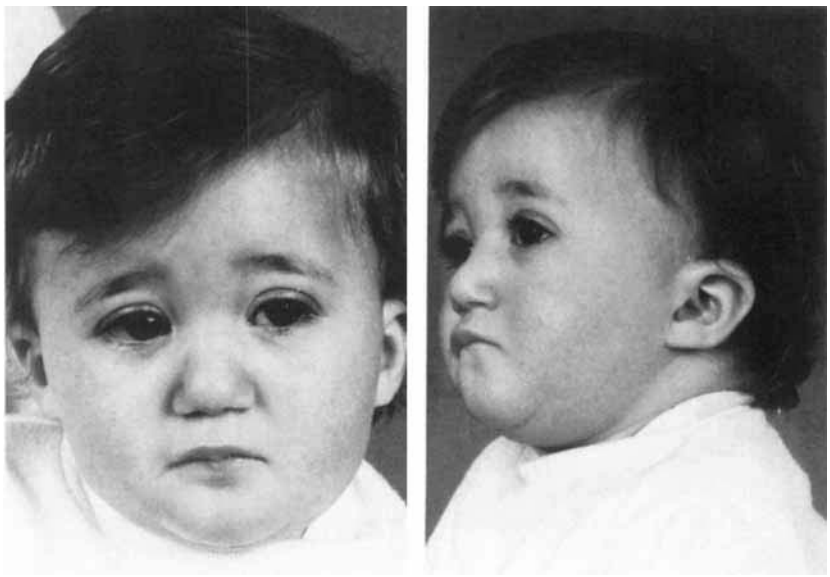

Figs. 1, 2. Patient age 18 months. Note deficient alae nasi, almond shaped palpebral fissures, bulbous nasal tip, and small "dysplastic" ears.

were present in both hands. Thumbs and toes were normal. A posterior cleft palate was present. A congenital heart defect was defined by ultrasound as a large perimembranous ventricular septal defect with some aneurysm tissue, 6 mm atrial septal defect with a normal aortic arch. Dyscoordinate swallowing and severe gastroesophageal reflux were treated by gastrostomy and fundoplication. Episodes of upper airway obstruction were shown to be due to tracheomalacia at bronchoscopy. The VSD and ASD where repaired and tracheopexy performed at 6 months. At operation the thymus was observed to be small and retracted superiorally.

INVESTIGATIONS

GTG-band analysis of blood leucocyte culture chromosomes showed a female karyotype with an interstitial deletion of 10p: i.e., 46,XX,del(10)(pter→p13::p12.2→qter) (Fig. 3). The parental chromosomes were normal.

In situ hybridization was performed with the cosmid probe N25, supplied by Oncor, Inc. (Gaithersburg, MD). The method supplied by the manufacturer was used and detection was with anti-digoxigenin-FITC on propidium iodine stained cells. Hybridization signals were detected on both of the chromosomes 22s in 15 metaphases examined. This indicates no deletion of locus D22S75 in this patient.

Pan-T cell markers were consistently at the lower limit of normal, while CD4, CD8, and CD19 counts where normal. T-cell proliferation in response to con A was reduced at age 6 weeks but normal at 14 months. T-cell proliferation was absent in response to Candida antigen, despite oral candidia. Serum immunoglobin levels (G,A,M) were normal. Serum calcium and renal ultrasound findings were normal.

DISCUSSION

The DiGeorge and the Velocardiofacial syndromes are manifestations of a similar developmental field defect of the 3rd and 4th pharyngeal pouches of the developing embryo and are associated with defects of migration of neural crest cells to the face, heart, thymus great vessels, and parathyroids [Lammer and Opitz, 1986; Conley et al., 1979; Goldberg et al., 1993; Lipson et al., 1991; Stevens et al., 1990]. The DiGeorge syndrome is usually designated when there is severe conotruncal congenital disease, thymic aplasia, and hypocalcaemia due to hypoparathyroidism [Lammer and Opitz, 1986; Conley et al., 1979]. However, VCFS can be associated with hypoparathyroidism, severe conotruncal congenital heart disease, and T-cell anomalies, [Lipson et al., 1991; Goldberg et al., 1985; Stevens et al., 1990] consistent with DiGeorge and VCFS being different expressions of the same condition. This was emphasised when Scambler et al. [1992] demonstrated that deletions on 22q, both microscopic and submicroscopic were associated with both syndromes. Less than 20% of VCFS and DiGeorge syndrome cases have cytogenetically detectable deletions on 22q11[Greenberg et al., 1988b; Driscoll et al., 1992]. Most of the remainder are shown to have a submicroscopic deletion on 22q11 by FISH and molecular techniques [Morrow et al., 1995 Driscoll et al., 1993 Goldberg et al., 1993; Levy-Mozziconacci et al., 1994]. A proportion do not appear to be associated with the deletion on 22q [Morrow et al., 1995; Driscoll et al., 1993]. The phenotype can be caused by teratogenic influences such as diabetes [Wilson et al., 1993], alcohol abuse [Amman et al., 1982], and vitamin A analogues such as isotretinoin [Lammer et al., 1985]. The phenotype has also been reported in an animal model by homologous inactivation of the HOXA 3 gene in mice [Chiska et al., 1991].

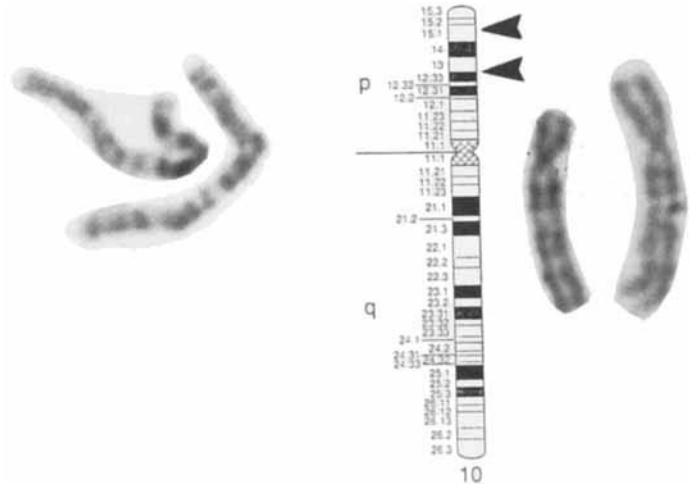

Fig. 3. Partial karyotype of normal and deleted chromosome 10.

DiGeorge syndrome has been associated with other cytogenetic abnormalities specifically del 4q21.3-q25 [Fukushima et al., 1992] isochromosome 18q [Van Essen et al., 1993] 17 p13 deletion [Greenberg et al., 1988b], monosomy 18q21.33 [Greenberg et al., 1988a], duplication 9q [Lindgren et al., 1993], duplication 1q [Vanden Berghe et al., 1973], and duplication 8q [Townes and White., 1978]. Compound cases include 10p deletion and duplication of 7p [Park et al., 1993], 10p deletion and duplication 5q [Lai et al., 1992], 10p deletion associated with two translocations [Kouseff et al., 1992], 10p deletion and trisomy 5q [Lai et al., 1992] and mosaic tetraploidy [Wullich et al., 1991] as well as a variety of rearrangements involving disruptions of 22q. After 22q11 deletions, 10p13 deletions are the commonest anomaly after 22q11 deletions as a cause of DiGeorge syndrome. In a cytogenetic study of malformations in 27,472 newborn infants, 537 had cytogenetic studies; 48 were abnormal of which 39 were trisomic and 9 had other cytogenetic anomalies, one being 10p13 deletion, an incidence of 0.04 per thousand livebirths [Higurashi et al., 1990]. No other estimate of the frequency of 10p13 is available.

Since our patient was not deleted on 22q by microscopic or FISH methods using the probe N25 which is probably in the critical deletion area [Morrow, 1995], there must be similar genes that control neural crest migration and development of the face, palate, heart, thymus, parathyroid glands, and renal tract in patients in the area of 10p13. Although our patient did not have manifest hypoparathyroidism, she had a cleft, congenital heart disease, T-cell defect, reduced Con A proliferation and absent reaction to Candida by Con A, dyscoordinate swallowing, small dysplastic ears, short stature, and developmental delay as seen in the 22q11 deletion syndromes [Lipson et al., 1991; Shprintzen et al., 1984; Goldberg et al., 1993; Levy-Mozziconacci et al., 1994]. Cleft lip occurs in VCFS caused by 22q deletion [Lipson et al., 1991] as well as 10p deletion [Park et al., 1993; Kouseff et al., 1992; Obregon et al., 1992; Shokeir et al., 1975]. Cleft palate alone, either overt or submucous, is a common anomaly in VCFS [Lipson et al., 1991; Goldberg et al., 1993]. Differences include small for gestational age at birth and hand anomalies, manifesting as contractures of the fingers. A variety of hand and limb anomalies have been reported with 10p deletion including syndactyly, preaxial polydactyly, club hand and foot, clinodactyly, broad and proximally implanted thumbs, and hypoplastic distal phalanges [Obregon et al., 1992;]. Contractures of the fingers, similar to this case, have been reported in two other cases of 10p13 deletion [Herve et al., 1984; Park et al., 1993]. The facial anomalies in our patient are similar to those seen in VCFS/DiGeorge, though there is some disagreement in the literature [Lynch et al., 1995].

These similarities in the phenotype and anomalies make it possible that 22q11 non deleted VCF/DiGeorge cases may be deleted at 10p13. Morrow et al. [1995] in a series of 61 VCFS patients found that 10 were not deleted on 22q11 by cytogenetic and molecular techniques. In our own series VCFS patients, two children with typical phenotype and deletions on 22q11 by N25 probe had further cytogenetic anomalies, one with 4p intestitial deletion and another with a balanced translocation between chromosomes 2 and 7. It may be possible that some single reports of cytogenetic anomalies associated with the VCF/DiGeorge syndrome, other than 10p or 22q, may represent a coincidental occurrence or additive abnormalities as none had submicroscopic deletions on 22q11 or 10p excluded. There is no indication which genes, when deleted on 22q or 10p, cause VCF/DiGeorge syndrome though several have been proposed [Wilson and Scambler., 1995; Morrow et al., 1995; Budarf et al., 1995]. The fibronectin receptor gene has been mapped to 10p12 [Wu et al., 1989; Goodfellow et al., 1989]. Fibronectin appears important in neural crest migratory behaviour [Newgreen and Tan, 1993] and thus is a candidate gene for this disorder, at least on 10p. A gene on 10p13 could be regulated by genes located on 10p12. Such a mechanism has been hypothesised for campomelic dysplasia, where balanced translocation breakpoints in infants with this disorder

where found to be 50→100 kb from SOX 9, the gene for this disorder [Foster et al., 1994; Wagner et al., 1994].

It is possible that some non deleted 22q11 VCFS/DiGeorge patients have a microdeletion at 10p13 particularly if they are small for gestational age at birth and have hand anomalies.

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